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## **Survival circuits in affective disorders**

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**Abstract**

Neuroscientific investigation of maladaptive learning in affective disorders has highlighted aberrant functioning of corticolimbic survival circuits. In particular, altered functioning of amygdala-prefrontal cortex circuitry has been demonstrated during acquisition and extinction of maladaptive conditional fears. Studies of psychological and pharmacological treatments for affective disorders demonstrate altered activation within the overlapping circuitries but suggest that the mechanisms of effects target different ‘access points’ within these circuits. Moving beyond the traditional boundaries of fear conditioning research, recent work has begun to investigate how positive valence systems (i.e., reward circuitry) contribute to maladaptive learning processes, and how effects vary across individuals with different diagnoses and subclinical presentations. Advances in this domain will be important for the development of future neuroscientifically-informed evidence-based treatments for affective disorders.

## **Affective Disorders**

Affective disorders encompass anxiety disorders (including post-traumatic stress disorder (PTSD)) and depressive disorders. Anxiety disorders are characterized by persistent, excessive fear, anxiety or avoidance of perceived threats, with different diagnoses associated with different threats (e.g., social situations in social anxiety disorder) [1]. PTSD is associated with heightened fear and avoidance based on traumatic events [PTSD was categorized as an anxiety disorder in DSM-IV, but is now separate in DSM-5; 2]. Depression is characterized by lowered mood and symptoms of anhedonia, the loss of interest, pleasure or motivation in previously rewarding activities. While these disorders are separated in clinical diagnostic manuals, comorbidity is estimated to be as high as 53% between anxiety and depression [3], 60% between PTSD and depression, and 85% between PTSD and anxiety [4]. Understanding how these disorders manifest and how they are maintained is a critical goal for the continued development of efficacious treatments.

Despite high rates of comorbidity, these disorders are typically studied in isolation, through different theoretical frameworks. However, investigation at the neurobiological level has revealed altered functioning in overlapping neural regions within ‘survival circuitries’. These regions include the amygdala, anterior cingulate cortex, ventral and dorsal prefrontal cortex, anterior insula and hippocampus and are implicated in anticipation, reactivity, regulation and learning of affective cues. The current review highlights commonalities and distinctions in disruptions to survival circuit functioning in affective disorders and how different treatment approaches impact functioning of these systems.

## **Neurobiology of anxiety disorders and PTSD**

The prevailing model of anxiety disorders focuses on maladaptive learning processes in relation to threat, a key construct within the Research Domain Criteria’s (RDoC) ‘negative valence system’ [5]. Translational research has demonstrated disruptions in the acquisition, extinction and recall of cue-threat associations in anxiety disorders and PTSD using fear conditioning paradigms. These laboratory paradigms pair previously innocuous stimuli, such as different colored lights, with aversive ‘unconditional stimuli’ (US), such as an electric shock, generating ‘conditional stimuli’ (CS). This allows investigation of associative learning between neutral cues never paired with the US (CS-) and threatening cues paired with the US (CS+; fear acquisition), updating or ‘extinction’ of these associations when ‘threat’ cues no longer predict aversive outcomes (CS+E; fear extinction) and memory for these associations (extinction recall).

Disruptions to these learning processes in individuals with anxiety disorders impact functioning of survival-relevant behavior across various domains, including orienting to threat, assessment of

threat and prediction strategies [6]. Relative to healthy adults, individuals with anxiety disorders/PTSD demonstrate increased fear responses to CS+, greater generalization of fear to stimuli that resemble the CS+, and increased fear responses to conditional safety cues (CS-) during fear acquisition [7-9]. During extinction, when CS+ is no longer paired with aversive US, individuals with anxiety disorders show stronger fear responses to CS+ than healthy individuals, resulting in delayed or reduced extinction [8-11]. Impaired extinction recall, primarily heightened responding to CS+E, has also been demonstrated in anxiety disorders and PTSD [9].

At the neurobiological level, affective learning processes are supported by cortical and subcortical circuitry, centered on the amygdala, prefrontal cortex (PFC) and hippocampus (see Figure 1). The structure and function of this circuitry has been shown to be disrupted in individuals with anxiety and PTSD. There is evidence of volumetric differences in the hippocampus, amygdala, ACC (PTSD only) and insula (anxiety disorders only) [12-14]. There is also evidence of differential activation and functional connectivity of the amygdala, insula, ACC and PFC in tasks involving threatening or emotional stimuli [e.g., 15]. Particularly within anxiety disorders, disrupted activation of PFC has also been demonstrated [16]. Investigation of maladaptive learning processes using fear conditioning paradigms have implicated altered functioning of amygdala, vmPFC and hippocampus during acquisition, extinction and extinction recall [for review, see 17].

Recent findings highlight a central role for amygdala-vmPFC connectivity in disrupted affective learning. Greater fear generalization among participants with PTSD was associated with increased amygdala activation and a decrease in amygdala-vmPFC functional connectivity from pre- to post-conditioning [18]. Among individuals with anxiety disorders, heightened vmPFC-amygdala connectivity and decreased vmPFC-subgenual ACC connectivity during fear acquisition predicted subsequent deficits in extinction recall [19].

*<insert figure 1 here>*

### **Neurobiology of Depression**

The study of depression has also highlighted heightened reactivity to negative stimuli, albeit to more general negatively valenced stimuli, rather than specifically to threatening stimuli. There is a wealth of evidence demonstrating a ‘negative bias’ in depression, where individuals attend more to negative cues, interpret ambiguous information more negatively and have a biased memory towards negative events [20]. In addition to disruptions in the negative valence system, anhedonia is a core feature of depression that is associated with deficits in anticipation, consumption and memory of rewarding stimuli [for review, see 21], a core aspect of the RDoC’s ‘positive valence system’ [5].

Notably, the network of brain regions shown to be disrupted in depression largely overlaps with the network of regions implicated in anxiety disorders and PTSD. These regions include the amygdala, hippocampus and ventral PFC (particularly the orbitofrontal cortex) [21-23]. Additional disruption to neural reactivity has been observed in depression among regions that make up the mesocorticolimbic dopamine pathway, including the ventral striatum and ventral tegmental area [22]. Deficits in the functioning of these regions have primarily been implicated in altered reward processing, particularly in relation to anticipatory and learning processes [21].

There is limited direct investigation comparing neurobiological correlates of anxiety and depression. One initial study suggests that individuals with major depressive disorder may have disruptions in fear acquisition [24]. This heightened reactivity to negative stimuli might be associated with disruptions in fear conditioning that resemble those seen in individuals with anxiety disorders. On the other hand, anhedonia is associated with overall ‘blunting’ of reactivity to affective stimuli, including deficits in anticipation, consumption and memory of rewarding stimuli [for review, see 21]. Anhedonic symptoms might impact fear learning in, as yet, uninvestigated ways. Another study compared individuals with panic disorder and agoraphobia with and without comorbid depression. Only those who did not have comorbid depression demonstrated enhanced activation of fear circuitry when processing safety signals, while those with comorbid depression demonstrated decreased dlPFC and insula activation during processing of CS+ or CS- [25]. This would suggest that neural substrates may alter quite substantially in the presence of depression, although much more research is needed.

### **Impact of treatments for affective disorders on survival circuitries**

Treatment studies afford the opportunity to investigate mechanisms of change, demonstrating how alterations in neural functioning are associated with improved psychological functioning. Mounting evidence suggests that pharmacological and psychological treatments effect change in survival circuitries. Both types of treatment have established efficacy in reducing overall levels of depression and anxiety, although many individuals fail to respond to treatment or experience residual symptoms at the end of treatment. Understanding the neurobiological mechanisms of treatment action can help to inform why, and for whom, these treatments are effective, knowledge which could be leveraged to inform personalized treatment decisions.

### **Psychological treatment mechanisms**

Cognitive behavioral therapy (CBT) is the most widely used and empirically supported psychological treatment for anxiety disorders [26], focusing on exposure to feared cues to promote extinction learning [27]. Studies of CBT for affective disorders have begun to demonstrate

treatment-related changes in activation and functional connectivity of key nodes of survival circuitry, including amygdala, ACC and medial/inferior prefrontal cortices [28-31].

A few of these studies have specifically assessed treatment-related changes in neural activation during fear conditioning. In one study, individuals with panic disorder and agoraphobia demonstrated reduced activation in inferior frontal gyrus and insula during fear acquisition from pre- to post-CBT [32]. Another study with a similar population demonstrated that reactivity to CS increased in lateral and medial prefrontal regions and the hippocampus, among those classified as ‘treatment responders’, compared to those who received less benefit from treatment [33]. In addition, a study of prolonged exposure for PTSD demonstrated reduced rostral ACC activation during extinction recall, as well as increased connectivity between this region and vmPFC/subgenual ACC from pre- to post-treatment [34]. While further understanding of these effects is clearly required, initial evidence suggests that psychological treatments for affective disorders alter activation in prefrontal cortical regions and the anterior cingulate cortex, suggesting a cortical ‘access point’ to modulate functioning of survival circuitries.

#### **Pharmacological treatment mechanisms**

Studies of pharmacological treatments for affective disorders have primarily focused on understanding the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) [35]. The recent neurocognitive model of antidepressant treatment action proposes that SSRIs effect change through diminishing negative bias in a ‘bottom-up’ manner, by altering amygdala and ACC reactivity to negative cues [36]. It is well established that the clinical response to SSRIs does not emerge until days or weeks after commencing treatment. The neurocognitive theory suggests that SSRIs effect change in negative bias soon after initial administration, but that repeated experience and learning processes may be required before changes in mood and cognitions develop. In support of this theory, one recent study demonstrated that *change* in amygdala, insula and ACC reactivity to emotional stimuli after 1-week of reboxetine administration was not related to initial changes in self-reported symptoms, but instead predicted change in symptoms after 6-weeks of treatment [37]. In contrast to psychological treatments that primarily impact cortical brain activity, evidence to date suggests that pharmacological treatments target subcortical regions of survival circuitry.

One recent study directly compared changes in neural functioning in response to CBT and SSRI treatment for panic disorder with agoraphobia [28]. Focusing on amygdala reactivity, both treatment types were found to reduce amygdala reactivity to agoraphobic stimuli, but this reduction was greater in the CBT group than the SSRI group. Given the hypothesis that pharmacological treatments target subcortical regions more directly than do psychological treatments, it might be

expected that greater reductions in amygdala reactivity would be expected in the SSRI group. Key to furthering understanding of this effect would be investigation of network dynamics in broader neural circuitries. We suggest that different treatments effect change in neural circuits through different ‘access points’. Modulating activity one region necessarily impacts functioning of other connected regions, thus understanding of differences in treatment action should encompass broad networks of regions and changes in connectivity over time.

### **Novel treatment approaches**

Advances in understanding of the neural substrates of affective disorders and mechanisms of treatment action have prompted development of novel treatment approaches. Harnessing the wealth of evidence demonstrating a central role for vmPFC functioning in extinction learning, researchers have begun to investigate whether manipulating activation within this region can impact the efficacy of extinction learning. Repeated transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method that can be used to increase electrical activation in targeted cortical brain regions. One recent study demonstrated that rTMS of the vmPFC accelerated extinction learning in individuals with acrophobia (fear of heights) when experiencing exposure in a virtual reality environment [38]. Although the authors report that these effects were not maintained at follow-up assessments, the efficacy at enhancing extinction learning suggests an interesting potential treatment adjunct for exposure therapy.

Another intriguing new area of intervention research for anxiety disorders is investigating whether fear responses can be effectively reduced without conscious experience of fear. One barrier to CBT efficacy is the focus on exposure to feared stimuli, an experience which can be unpleasant for the patient, and contributes to avoidance. Recent work has investigated whether neurofeedback can be used to generate patterns of brain activity associated with feared stimuli, in the absence of conscious awareness, and then paired with rewarding stimuli to counter-condition fear responses [39]. These procedures rely on machine learning methods of multivoxel pattern analysis and provide feedback to the participant on whether they are achieving the required brain state or not. Importantly, participants are given no explicit instructions on how to achieve this brain state. In just three training sessions, authors demonstrated that experimentally-induced fear was effectively reduced using neurofeedback. Future investigation of whether this approach can also effectively reduce pathological anxiety will be of much interest [39].

### **A role for reward circuitries in maladaptive learning**

Anxiety disorders/PTSD have been conceptualized mostly from the framework of threat-processing, but recent attention has been given to the role of reward-processing, particularly in



relation to avoidance behavior. Avoidance of feared cues or situations is a core feature of anxiety disorders/PTSD, it presents a barrier to extinction learning and is considered a primary contributor to clinical impairment [40]. Yet, there has been less research investigating avoidance than the acquisition and extinction of excessive fears [41]. The decision to engage in avoidance behaviors is driven by the potential negative value of a feared stimulus, but at the same time these behaviors are likely to be reinforced by the positive value of ‘relief’, after successfully avoiding a feared stimulus [42]. In support, expression of ‘avoidance’ of a US (via pressing a button) was associated with increased activation of the ventral striatum [43], a region of the reward system with an established role in signaling prediction error [22]. It has been suggested that elevated expectancies of negative outcomes might incur greater relief responses among individuals with anxiety disorders. Augmented ‘relief-reward’ could be one mechanism through which avoidance behaviors are reinforced in anxiety disorders [44].

Interactions between disrupted threat and reward processes may be particularly important to consider given the high proportion of individuals experiencing comorbid anxiety/PTSD and depression. In particular, given blunted reward responses in depression, it is plausible that the reinforcement value of relief in individuals with comorbid anxiety and depression may be reduced compared to those with only an anxiety disorder. Better understanding of these, and other, patterns of disrupted motivation and reinforcement may be key to determining the mechanisms of how affective disorders and maladaptive responding are maintained in psychopathology. Consideration of transdiagnostic features of affective disorders has the potential to transform the development of novel treatment strategies. For example, we recently developed a novel behavioral treatment for anhedonia aiming to target neuro-scientifically identified deficits in reward processing in depression: anticipation, consumption and learning of reward [45] with the goal of improving symptoms of anhedonia. Initial results are promising, demonstrating an improvement in positive affect and reduction in symptoms of anxiety and depression [46].

## **Conclusion**

The clinical neuroscience of fear conditioning is one example of the benefits of interdisciplinary mental health research, whereby mechanistic understanding of maladaptive learning can inform development of more efficacious treatment. Evidence to date implicates altered functioning of [survival circuitries in affective disorders, particularly](#) amygdala-PFC circuitry, while depression is more specifically associated with altered functioning of reward regions. Treatment studies for affective disorders suggest that psychological and pharmacological treatments effect change in cortico-amygdala circuitries through different mechanisms, with psychological treatments primarily impacting functioning of cortical regions and pharmacological approaches targeting

subcortical regions. Recent work has begun to leverage understanding of disrupted neurobiological functioning in affective disorders to develop novel treatment approaches, such as noninvasive cortical stimulation and neurofeedback. Greater communication between neuroscientists and clinical researchers will be key to the future of translational research in affective disorders, including combined investigation of neural circuitries for threat- and reward-related behaviors for a more comprehensive understanding of how maladaptive behaviors are maintained.

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**Conflict of interest statement**

Declarations of interest: none

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### *Annotated reference*

\*Marin et al., 2017, JAMA Psychiatry

A large study of neural correlates of fear learning in anxiety disorders, demonstrating reduced vmPFC activation compared to healthy individuals during fear acquisition and an imbalance in vmPFC connectivity, favoring amygdala connectivity over sgACC connectivity. Notably, this connectivity predicted performance during extinction recall, highlighting a central role of neural functioning within this circuitry in fear learning and extinction.

\*Morey et al., 2015, Translational Psychiatry

A carefully designed study demonstrating within-subject changes in neural connectivity within survival circuitry in relation to safety learning. Trauma exposed control participants demonstrated increased amygdala-vmpfc connectivity, associated with successful safety learning, while individuals with PTSD showed heightened fear responses and no such increases in connectivity.

\*Liebscher et al., 2016, European Neuropsychopharmacology

This treatment study demonstrates the potential for investigation of the neuroscientific mechanisms of psychological therapies. Individuals with panic disorder/agoraphobia were shown to demonstrate reduced amygdala activation when viewing agoraphobia-related images, compared to either healthy controls or patients treated with SSRI/SNRIs.

\*\*Vervliet et al., 2017, Behavior Research and Therapy

This novel paradigm demonstrated the role of ‘relief’ in reinforcing avoidance behaviors in a novel conditioning paradigm, with participants low in ‘distress-tolerance’ demonstrating sustained relief responses. These findings support suggestions that avoidance behaviors might be maintained through the reward value of relief.

\*\*Craske et al., 2016, Depression and Anxiety

This paper details the development and rationale for developing a novel treatment for anhedonia, grounded in neuroscientific understanding of reward processing deficits. This transdiagnostic treatment strategy is one example of how findings across clinical and neuroscientific researcher can be combined to target unmet therapeutic needs.

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## Figure captions

Figure 1. **Left:** Neural circuitries supporting fear conditioning. Feedforward connectivity from the amygdala propagates to hippocampus and prefrontal cortex for integration with other sensory information and encoding of contextual cues. Feedback connectivity from prefrontal regions (e.g., vmPFC/sgACC) is thought to ‘down-regulate’ amygdala activation, important for diminishing threat reactivity to ‘safe’ cues (CS-) [47, 48]. **Middle:** Regions shown to have altered activation during fear acquisition, extinction or recall among individuals with anxiety disorders and PTSD. Red arrows denote altered connectivity among regions (amygdala-vmPFC; vmPFC-sgACC;[19]). **Right:** Regions showing differential activation among individuals with anxiety disorders or PTSD after cognitive behavioral therapy during fear acquisition, extinction or recall. Treatment studies demonstrate changes in lateral and superior regions of PFC that are not typically implicated in fear conditioning or disrupted in affective disorders.